**REMARKS**

On behalf of the Applicants, the undersigned wishes to express appreciation for the telephonic interviews granted on November 15, 2004 with the Examiner and his supervisor and again on November 16, 2004 and December 15, 2004, with the Examiner. A number of issues were discussed. These interviews have been very helpful and it is believed that they reduced the number of issues remaining in the application.

During the December 15, 2004 interview, the Examiner indicated that he had no problems with claims similar to Claims 69 and 70 but he still was of the opinion that Claim 68 was obvious over the combination of Makooi-Morehead et al (U.S. Patent 6 238 695) and Elger et al (U.S. Patent 4 844 407). He also indicated that he would give favorable consideration to a showing (Declaration) that the use of any two of the compounds recited in Claim 70 (each in a separate composition) would result in a composition having increased bioavailability.

Claims 2-20, 22-24, 26, 34, 36, 68, 70 and 71 are in the application, Claims 37 and 69 being canceled and Claim 71 being added by this amendment.

Claims 2-20, 22-24, 26, 34, 36, 68 and 70 stand finally rejected under 35 U.S.C. §103(a) "as being unpatentable" over Makooi-Morehead et al, either alone or in view of Elger et al.

Claim 68 has been amended by adding the limitation "without heat, solvent or grinding". This amendment makes Claim 69 a duplicate of Claim 68, so Claim 69 has been canceled.

New Claim 71 is similar to Claim 68 but limits the "fairly soluble or highly soluble salt" to a "fairly or highly soluble salt of a free base". The use of "fairly soluble or highly soluble salts of free bases" is disclosed in the specification and original claims so this limitation does not introduce new matter into the application.

Entry of the amendments is respectfully requested.

THE REJECTION OF CLAIMS 2-20, 22-24, 26, 34, 36, 38, 68 AND 70 UNDER 35 U.S.C. §103(A) AS BEING UNPATENTABLE OVER MAKOOI-MOREHEAD ET AL (U.S. PATENT 6 238 695) IN VIEW OF ELGER ET AL (U.S. PATENT 4 844 907)

While the references used in the final rejection are the same as those used in prior rejections, the Examiner has applied them in a manner that constitutes alternative rejections and, hence, includes a new ground of rejection. Therefore, I will address both rejections. The first is a rejection of all of the claims over the combination of Makooi-Morehead et al and Elger et al and the second is a rejection of all of the claims, except Claim 70 which recites specific active pharmaceutical ingredients, over Makooi-Morehead et al alone.

THE REJECTION OF CLAIMS 3-20, 22-24, 26, 34, 36-38, 68,69 AND 70 OVER MAKOOI-MOREHEAD IN VIEW OF ELGER ET AL

Present Claim 68 is patentably distinguishable over the combination of Makooi-Morehead et al and Elger et al for the following reasons:

Present Claim 68 is directed to a non-sustained release, non-chewable tablet composition comprising:

(a) a rapidly precipitating drug which is a fairly soluble or highly soluble salt form of a poorly soluble free base or free acid that is prone to supersaturation when introduced in water or simulated physiological fluid at body temperature, and more than 90% of it precipitates out within 60 min after coming into contact with said water or simulated physiological fluid at body temperature, with the proviso that the drug is not delavirdine mesylate, is the sole active pharmaceutical ingredient in said composition and is present in an amount from about 5 to about 60%;

(b) a polymeric binder; present in an amount of from 2 to about 25%;

(c) a superdisintegrant in an amount from about 6 to about 40%; and

(d) a lubricant present in an amount up to about 5%; and wherein the rapidly precipitating drug, polymeric binder, superdisintegrant and lubricant are mixed and compressed into a tablet without heating, solvent or grinding.

While limiting Claim 68 to specific polymeric binders and superdisintegrants recited in some of the dependent claims was discussed during the telephonic interviews, upon further review with Applicants this limitation has not been added to the claim.

Also it was earlier stated that the recitation "without heat, solvent or grinding" excluded "wet-granulation". However, this language is recited in the claim not to exclude tablet compositions made by wet granulation techniques but to differentiate the claimed tablet composition from tablet compositions that are made by using solid dispersion techniques such as co-precipitation via heating, solvent use or grinding to achieve co-precipitation as is discussed on page 1, lines 21-28 of the instant specification. During wet granulation, particle surfaces are wetted but the particles are not dissolved. Therefore, wet granulation is not a process that involves the use of heat, solvent or grinding.

Applicants have stated clearly on the record why they do not believe there is motivation to combine the teachings of Makooi-Morehead et al and Elger et al to render the claimed composition obvious. These reasons are outlined in detail in points (a) through (e) in the paragraph bridging pages 19 and 20 of Applicants' Response dated August 20, 2005. The Examiner has presented no evidence or other reasons supported by the record that refutes the fact that Makooi-Morehead et al and Elger et al are trying to solve different problems. Furthermore, the Examiner's suggestions that Elger et al

utilizes a lubricant of the type used by Makooi-Morehead et al and, hence, would be compatible in combination with Makooi-Morehead et al simply is not supported by the evidence of record. Elger et al is replete with failed examples when lubricants of the type used in Makooi-Morehead et al are used in their tablet compositions. See Comparative Examples A-D in columns 5, 6 and 7. The crux of Elger et al's invention is the use of "self-lubricating" compression aids rather than conventional lubricants. Because there would be no motivation to combine Makooi-Morehead et al and Elger et al, the Examiner has not presented evidence or reasons that overcome Applicants' arguments and therefore still has failed to establish a prima facie case of obviousness.

Neither Makooi-Morehead et al nor Elger et al, alone or in combination, teach or suggest using an active pharmaceutical ingredient that is prone to supersaturation in water or physiological fluids at body temperature. Therefore, even if Makooi-Morehead et al were properly combined with Elger et al, the combination would still fail to teach all of the limitations of Claim 1 and therefore renders the claimed tablet composition non-obvious.

Claims 2-20, 22-24, 26, 34, 36, and 70 contain all of the limitations of Claim 68, so they are patentable over the combination of Makooi-Morehead et al for the reason that Claim 68 is and because they contain additional limitations that further define them over the combination of references.

New Claim 71 is similar to present Claim 68 but it further requires that the "fairly soluble or highly soluble salt form" be a "fairly soluble or highly soluble salt form" of a free base. The compound Efavirenz is a free acid, as is shown by the 37 CFR 1.132 Declaration of Dr. Walter Morozowich, one of the Applicants in the above-captioned application. Even if Efavirenz formed a salt, the salt would

be that of a free acid. Since Claim 71 contains all of the limitations of Claim 68, it is patentable over the combination of Makooi-Morehead et al and Elger et al for the reasons that Claim 68 is and for the additional reason that it limits the salt form to a salt of a free base.

It is the opinion Dr. Morozowich, an expert in the area of pharmaceutical formulations, that Efavirenz is unlikely to form a salt that would form a supersaturated solution. Therefore, even if Makooi-Morehead et al were properly combined with Elger et al, the combination would still fail to teach all of the limitations of the tablet composition defined in Claim 71.

While the above discussion sets forth the reasons that the tablet of Claim 1 is patentable over the combination of Makooi-Morehead et al and Elger et al, Applicants now address specific arguments made by the Examiner in the Office Action of November 17, 2004.

In explaining how the references are being combined, the Examiner gives seemingly conflicting reasons.

First, in the paragraph bridging pages 2 and 3, he states:

> "Here, the modifications of Makooi-Morehead are merely based on substituting the active drug recited in Elger. Such modifications are based on what the state of art of pharmaceutical formulation is and what is construed from the teachings of Makooi-Morehead and Elger by one of ordinary skill in the art. Examiner has taken the position that the modifications described flow naturally from the suggestions of the prior art as all elements of the instant claims are described by the cited references."

Based upon this reasoning, one skilled in the art would substitute two active pharmaceutical ingredients, an analgesic and an anti-inflammatory agent, for a single active pharmaceutical ingredient, Efavirenz. Therefore, contrary to the Examiner's assertion, such a combination would still fail

to meet all of the limitations of Claim 1 because Claim 1 is limited to a tablet composition containing a single active pharmaceutical ingredient. This illustrates again that Elger et al and Makooi-Morehead et al are trying to solve different problems and, hence, are not combinable to support a 35 USC 103(a) rejection of Claim 1.

Second, on page 5, first full paragraph, the Examiner states,

> "Second, the rejection of record merely uses Elger to show that for purposes of preparing a tablet, the salt forms of rapidly precipitating drugs that fall within the scope of instant claims are essentially functional equivalents to their free base or free acids forms. Note for example the recitation of narcotic analgesics such as hydromorphone or its hydrochloride salts as preferred form. (col 2, lines 4-15)."

The Examiner's statement that free acid and base forms are "essentially functional equivalents" of the salts defined in Claim 1 is merely a conclusion and not supported by any evidence of record. While Elger et al discloses that parent compounds and their salts can be used in their bilayered tablets, they do not recognize or teach the advantage of utilizing a salt form of a drug that is prone to supersaturation over a parent drug that cannot form a supersaturated solution. A free base or acid that is not capable of forming a supersaturated solution in water or physiological fluids at body temperature is not a functional equivalent of the salt form, in the context of the claimed tablet, of one that will because it does provide the same high bioavailability.

In further support of the propriety of the combination of references, the Examiner states on page 3, second full paragraph,

> "In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

> are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); …"

While the Examiner's quotation of the principle enunciated in the case is correct, his application of it is not. References have to be analyzed individually to determine if they are combinable.

In the paragraph bridging pages 3 and 4, the Examiner asserts that "applicant appears to be mischaracterizing the teachings of Makooi-Morehead as two sets of teaching that are directed away from each other." In the first paragraph on page 4, the Examiner asserts,

> "Here, Applicant appears to misinterpret what it means to "teach away" from a patented invention. Generally, "disclosed examples and preferred embodiments do not constitute a teaching which is away from a broader disclosure or nonpreferred embodiments.""

The Examiner has misconstrued Applicants' argument. Applicants' position is that Makooi-Morehead et al and Elger et al teach away from each other and, hence, are not properly combinable. It is improper to combine references where the references teach away from their combination, *In re Grasseli*, 218 USPQ 769, 779 (Fed. Cir. 1983). Furthermore, Applicants are not relying on preferred embodiments or examples for the teaching away of the use of conventional lubricants. They are relying on the general teaching in Elger et al that self-lubricating compression aids and non-conventional lubricants such as stearic acid and stearate salts are used in Elger et al's tablet compositions. See Column 1, lines 34-40 and lines 49-66, and Column 3, lines 26-42, where they state,

> "Having made this observation, the present inventors then overcame these problems by an inventive combination of devices. These were …
>
> (ii) Removing stearic acid and/or stearate salts (especially magnesium stearate) from the composition, and …"

This general teaching away is supported by the failed examples wherein magnesium stearate was used as the lubricant.

## THE REJECTION OF CLAIMS 2-20, 22-24, 26, 34, 36, 68 AND 70 UNDER 35 USC 103(A) AS BEING OBVIOUS OVER MAKOOI-MOREHEAD ET AL ALONE

In this rejection, the examiner raises for the first time the issue of whether or not Makooi-Morehead et al alone discloses or suggests the use of a fairly soluble or highly soluble salt of Efavirenz. In raising this issue, he notes that Makooi-Morehead et al incorporates by reference the teachings of U.S. Patent 5 519 021 (the '021 Patent) and concludes, "The teachings in US '021 is also directed to all suitable salts of Efavirenz (see US '021 at abstract examples 1-8, claims 1-10)."

However, none of these places in the '021 patent disclose or suggest that any salt of Efavirenz would form a supersaturated solution in water or physiological fluids at body temperature. The abstract simply says that disclosed compounds can be "used either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients."

The claims of the '021 patent all recite the phrase "or a pharmaceutical acceptable salt thereof".

This generic mentioning of salts encompasses a wide variety of salts, whether or not they may be capable of forming a supersaturated solution such as required of the tablet composition defined in Claim 68. This disclosure includes inorganic salts such as the sodium, potassium and lithium salts, all of which Dr. Morozowich opines in his Declaration will not form supersaturated solutions.

With respect to the examples in the '021 patent, there are six and none are directed to a salt let alone a fairly soluble or highly soluble salt that is prone to

supersaturation in water or physiological fluids at body temperature.

A generic reference to a large group or class of compounds does not render obvious specific compounds of that group that exhibit unexpected results (*In re Jones*, 21 USPQ 2d 1941 Fed. Cir, 1991; *In re Baird*, 29 USPQ 2d 1550). In the instant case, a reference to a broad group of "pharmaceutically acceptable salts" is not a teaching of the use of a pharmaceutically acceptable salt that will form a supersaturated solution in water or physiological fluids at body temperature. In fact, no named salt of Efavirenz is disclosed.

The Examiner's concluding remark about Makooi-Morehead et al is that,

> "Makooi-Morehead shows all elements of the instant claims except the exact drugs recited in claim 70. Makooi-Morehead uses Efavirenz with lactose; a flow agent, such as colloidal silicon dioxide; a superdisintegrants, such as croscarmellose and sodium glycolate, and a binder, such as microcrystalline. Makooi teaches that such combination of ingredients improves the rate of dissolution and thus the extent of absorption in the GI-track, (col 2, lines 3-7). Accordingly utilizing them and further optimizing their concentrations for desired rate and extent of absorption is well within purview of an ordinary artisan (see col 5, line 40 - col 6, line 16; col 7, line 15 - col 8, line 33)."

However, a close reading of Makooi-Morehead et al reveals that not only do they not teach a single salt of Efavirenz or suggest that any salt of Efavirenz is prone to supersaturation, they do not disclose the use of a polymeric binder as is required by Claim 68. In Makooi-Morehead et al's only exemplification of a tablet, Example 3, the binder is hydrous lactose (not microcrystalline cellulose), which is not a polymeric binder, as has been pointed out by Applicants in their Response of July 8, 2003. In the paragraph bridging pages 19 and 20 of that Response, Applicants stated the following:

> "As explained by Dr. Martino during the telephonic interview, the binders described in the Makooi-Morehead patent are comprised of lactose, starch and various sugars (Column 3, lines 21-22). In the current common state of the art, these materials are more often considered to function primarily as diluents, since in their native forms their components merely provided a limited degree of tablet bond. In contrast, the term binder as used in our claims is the generally more effective polymeric binders as disclosed on page 4, lines 21 and 22 of the specification, wherein it is stated:
>
> > "It is apparent to those skilled in the art that the binders of the present invention are polymeric binders as opposed to non-polymeric binders.""

With respect to microcrystalline cellulose, Applicants also provided in their Response of July 8, 2003 evidence that it does not delay precipitation.

The unobviousness of the claimed invention resides in Applicants' selection (1) of a specific form of the drug (a fairly soluble or highly soluble salt of a poorly soluble free base) that is prone to supersaturation and (2) a combination of the drug form with specific amounts of a polymeric binder and a superdisintegrant that delays precipitation of the drug from the supersaturated solution.

Claims 2-20, 22-24, 26, 34, 36, and 70 contain all of the limitations of Claim 68 so they are patentable over Makooi-Morehead et al for the reason that Claim 68 is and because they contain additional limitations that further define over the combination of references.

New Claim 71 contains all of the limitations of Claim 68 so it is patentable over Makooi-Morehead et al for the reasons that Claim 68 is and for the additional reason that it limits the fairly or highly soluble salt to the salt of a free base and, as pointed out above, any salt of Efavirenz would be the salt of a free acid.

Also provided with this Response is a supplemental Information Disclosure Statement.

In view of the above amendments, the Declaration Under 37 CFR 1.132 and arguments, withdrawal of the final rejection and expeditious passage of this application to issue is respectfully solicited.

Respectfully submitted,

Sidney B. Williams, Jr.

SBW/smd

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Encl: Information Disclosure Statement
37 CFR 1.132 Declaration of Dr. Walter Morozowich
Postal Card

136.0703

PATENT APPLICATION

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: Alice C. MARTINO et al
For: TABLET FORMULATION
Serial No.: 09/656 364 Group: 1617
Confirmation No.: 3730
Filed: September 6, 2000 Examiner: Sharareh
Atty. Docket No.: Pharmacia Case 6107.N CN2

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**DECLARATION OF DR. WALTER MOROZOWICH**
**UNDER 37 CFR 1.132**

I, Walter Morozowich, the undersigned, declare as follows:

That, I received a B.S. degree in Pharmacy from Duquesne University, Pittsburgh, PA in 1955;

That, I received an M.S. in Pharmaceutical Chemistry in 1956 and a Ph.D. in Pharmaceutical Chemistry in 1959, both from Ohio State University, Columbus, OH;

That, I joined the Pharmacy Research Unit of the Upjohn Company in 1959 where I worked until 1984 on Salt Synthesis and Prodrug Synthesis;

That, I have worked on the following project assignments since 1984:

1984 - 1989
Lymphatic Drug Targeting, Intestinal Absorption Assessment
1989 - 1993
Dog Gastroduodenal Fistulated Model Development, Pre-clinical
Candidate Selection and Preformulation Development
1993 - 1995
Softgeland Microemulsion Formulation Dev.

1996 - 1998

Salt Selection, Intrinsic Dissolution Rate Studies

1998 - 2000

Experimental Formulations

1998 - 1999

SEC Formulation, Diffusion Layer Modulated Powders

2000 - Present

Consultant, SEDDS, S-SEDDS Formulations, Prodrugs

That, I am one of the co-applicants in the above captioned case;

That, I am aware of U.S. Patent No. 6 238 695 (Makooi-Morehead et al) which claims a tablet composition that contains the active pharmaceutical ingredient Efavirenz;

That, the pH of the small intestines, where orally administered drugs are absorbed, is about 6-8;

That, Efavirenz is a free acid drug that has an experimental pKa of 10.2 and its solubility increases only above pH 10.2;

That additional information on Efavirenz is shown on Exhibit A which is attached and made a part of this declaration;

That, because of its high pKa, it will be difficult to prepare conventional salts of Efavirenz with amines;

That, inorganic salts of Efavirenz, such as the sodium, potassium, and lithium salts could be prepared but they should undergo a spontaneous "salt hydrolysis" upon contact with water or physiological fluids leading to immediate precipitation of Efavirenz without generation of a supersaturated state;

That, Efavirenz is a free acid and any salt of it probably will not generate a supersaturated state because of rapid conversion to the parent free acid.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true and further the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Date: May 19, 2005

Walter Morozowich

EXHIBIT A

The experimental pKa of Efavirenz is 10.2 (acid) and the solubility increases only above pH 10.2. (See: Determination of the pKa and pH-solubility behavior of an ionizable cyclic carbamate, (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one(DMP 266) (Efavirenz). Rabel, Shelley R.; Maurin, Michael B.; Rowe, Susan M.; Hussain, Munir. Pharmaceutical Development and Technology (1996), 1(1), 91-95. The web site is: http://www.aapspharmsci.org/ps0304/ps030428/ps030428.pdf).